## REMARKS

A restriction/ election requirement under 35 U.S.C. §121 was mailed to Applicants' Attorney on May 25, 2006 and this Required that Applicants elect and invention from claim groups I-IV which consisted of the following:

| Inventions | Classification |
|---|---|
| Group I.- claims 1-6, 14 and 15 drawn to a chemical compound and a pharmaceutical composition of formula I. | Not provided |
| Group II - claim 7 drawn to a medicament comprising a chemical compound of formula I. | Not provided |
| Group III - claims 8-13 drawn to a method of treatment of various disorders using a chemical compound of formula I. | Not provided |
| Group IV. - claims 8-13 drawn to a method of prophylaxis of various disorders using chemical compound of formula I. | Not provided |

In the second response to the restriction requirement mailed August 23, 2006, Applicants provisionally elected the invention of Group I with traverse, namely, claims 1-6, 14 and 15 drawn to a chemical compound and a pharmaceutical composition of formula I. Additionally, Applicants also elected with traverse a sub-generic species falling within the scope of invention Group I to be a compound of formula I, wherein $R_1 = R_3 = R_6 = R_7 = R_8$ = hydrogen, $R_2 = R_4$ = halogen, $R_5$ = alkyl, $R_9$ = L-G, wherein L = $NR_{30}CO$-, and G = $C_a(OR_{32})_XH_{2a+1-x}$, wherein $R_{30} = R_{32}$ = hydrogen and x = a = 5. A single specific compound falling within this species is N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide, which is described in Example 2 at line 42, page 43 to line 22, page 44 of the specification.

Despite fact that the election of the genus and species in response to the restriction requirement was made with traverse and valid arguments in support thereof

were made of record, the Examiner has continued to maintain that the election requirement under 35 U.S.C. § 121 was proper and has made it final. Objection to this final holding is still traversed for purpose of appeal.

Claims 1-15 as filed were pending in the present application prior to the submission of this amendment and response. As discussed in the preamble of this submission, original and amended claims 1-15 submitted in the previous response of 12/4/06 have been cancelled. Original claims 1-4 (now 16-19) have been amended in order to limit the compounds claimed to those structures wherein L is selected from the group comprising –NR30CO-, CONR30, -NR30CONR31 and –NR30COO – so as to recite compounds that are specifically disclosed in and supported by the specification and, in particular, the examples.

Original claims 2-6 (now 17-21) have also been amended whereby the language " pharmaceutically acceptable salt or trifluoroacetate of said compound ..." has been deleted so as to remove the redundancy that existed through their dependence on claim 1 (now 16) which already recited that limitation and was duplicative thereof.

It is asserted that members of a claimed Markush group must share a common unity of inventions whereby the claimed compounds share or common utility and also share a substituted structural feature that is disclosed as being essential to that utility.

The Examiner has rejected elected original claims 1-7 (now 16-22), 14 and 15 (now cancelled) on the grounds that they are drawn to an improper Markush group. It is asserted that members of a claimed Markush group must share a common unity of inventions whereby the claimed compounds share or common utility and also share a substituted structural feature that is disclosed as being essential to that utility It is their further asserted that the claimed subject matter of new claims 16-22, do not share a substantial structural feature disclosed as being essential to a given utility. The rejection of claims 1-7 (new claims 16-22) is respectfully traversed for the following reasons.

It is humbly submitted that the claimed compounds do in fact share unity of invention since they share a common structure (4-phenyltetrahydroisochinoline) with a hydrophilic side chain L-G. The compounds also share a common utility as all are

sodium/hydrogen exchanger molecules type-3 (NHE-3) which are useful in the treatment of a number of diverse diseases as recited in claim 23, i.e., respiratory disorders, central nervous system diseases, renal failure, diabetes, transplant rejection and the like.

However, in order to expedite the prosecution of the pending claims and facilitate examination, claim 1 has been amended whereby the Markush group of R7, R8 and R9 which have been defined as an L-G group are now more specifically limited. The definition of L in claim 1 is now limited to –NR30CO-, -CONR30-. –NR30CONR31 and NR30COO-. As all of these compounds are NHE3 inhibitors useful in the treatment of a specific number of CNS-related and metabolic diseases, the two prong test for unity of invention, i.e., a) common utility and b) a shared substantial structural feature essential to that utility has been met. The Examiners' rejection of claims 16-22 must therefore respectfully be withdrawn.

Rejection under 35 U.S.C. §103 (a)

The Examiner has rejected claims 16-22, as being unpatentable for obviousness under 35 U.S.C. §103 (a) in view of PCT/US00/30328 to Beck et al. It is asserted that the claimed compounds herein are already taught in Beck et al '30328 in the formula at pages 3-5 and at Table A on page 14. It is asserted that the only difference between the present compounds at issue and the prior art compounds is the selection of various radical groups which are substituted at different positions on the molecule.

The Examiner has further concluded that the Beck et al reference teaches the equivalence of H and –NHC(O)- which are substituted on the phenyl ring. It therefore would have been obvious to one having ordinary skill in the art at the time the invention was made to modify any one of the compounds of Table C of Beck et al.,accordingly.One of ordinary skill in the art would have been motivated to do this in order to obtain another of the pharmaceutical compounds preferred by Beck et al., especially since the reference clearly suggested that such substitutions would produce a compound with similar properties. The Examiner therefore concludes that based upon the teachings of Beck et al, one of ordinary skill in the art of general chemistry would expect that modifying one radical for another would not change the properties of a compound in a significant way.

As such, the instantly claimed compounds are unpatentable thereover. The rejection is respectfully traversed for the following reasons.

Whereas there are many compounds that comprise the generic class, some tetrahydroisoquinolines are known to be inhibitors of the sodium/hydrogen exchanger (NHE). The specification of the present application at page 31 et. seq. makes it clear that compounds of the present invention exhibit superior inhibitory properties of the sodium-hydrogen ion exchanger channel of the subtype 3 (NHE-3). The NHE-3 channel is found in vivo, and in particular, in the cells of the brain, gallbladder, intestines and the kidney.

As a consequence of their unexpected NHE-inhibitory properties, the compounds of the formula I are suitable for preventing and treating disorders which are caused by the activation of and/or by an activated NHE. The use of the inventive compounds relates to the prevention and treatment of acute and chronic disorders in human and veterinary medicine..

As a result of the pharmacological properties of the substituted 4-phenyl tetrahydroisoquinoline compounds of the present invention, they are useful as anti-arrythimic agents for the treatment and cardio-protection against arrythmic infarction and cardiovascular ischemia. They also provide cardio-protective benefits to the heart, blood and cardiopulmonary systems.

These compounds have also been shown to provide protective action against ischemia-induced damage in the central nervous system (CNS) and can thereby prevent or treat stroke and cerebral edema. Respiratory disorders (sleep apnea, hypoxia, hypercapnia), epilepsy, depression, psychological neroses, and anxiety disorders can all be treated with one or more of these compounds, their salts and variants thereof.

Upon a closer look, Beck et al. claims 4-phenyltetrahydroisoquinolines with very broad and generic definitions and the use thereof to block reuptake of norepinephrine, dopamine and serotonin which makes them useful in the treatment of various neurological and psychiatric disorders. Therefore, the properties and the use of these compounds are not related in any way to the use of the present claimed inventive compounds as NHE-3 inhibitors, for example for the treatment of sleep apnea, cardiovascular ischemia, and/or CNS disorders. Additionally, the compounds claimed in Beck et al. can never be defined carrying a hydrophilic side chain –L-G on the phenyl

ring as it is the case in the present invention. It is not possible to construe or interpret substituents R5, R6 and R7 to be defined as the hydrophilic group, –L-G. Furthermore, the compounds disclosed in the Beck et al. examples are not related to present disclosed/claimed compounds of formula I except for the fact that they are similar to 4-phenyltetrahydroisochinolines. Therefore, these compounds cannot be said to motivate a person skilled in the art to invent 4-phenyl-substituted tetrahydroisoquinolines with a hydrophilic side chain L-G.

The rejection of new claims 16-22 under 35 U.S.C. §103 for obviousness in view of Beck et al '30328 must also be respectfully be withdrawn.

Rejection for Double Patenting

The Examiner has rejected original claims 1-7 (new 16-22) on the ground of non-statutory double patenting over the claims of U.S. Patent No. 6,703,405 also to Hofmeister et. al. It is asserted that the subject matter claimed in the instant application is fully disclosed in the '405 patent since both the application and the issued patent recite the same subject matter which therefore over-laps. The Examiner then points specifically to the definition of the radicals R7,R8, and R9 that are attached to the phenyl ring. Whereas it is offered that the double patenting rejection may be possibly removed with the timely filing of a terminal disclaimer giving up any patent term beyond that of December 20, 2022, the Examiners rejection for double patenting is respectfully traversed for the following reasons.

It is respectfully asserted that the claims of Hofmeister et al '405 and the present claims as amended do not over-lap or read-upon one another in any way. The cited prior art Hofmeister patent claims substituted, 4-phenyltetrahydroisoquinoline salts which by their very definition cannot carry a hydrophilic side chain L-G on the phenyl ring where L is selected from the group comprising $–NR_{30}CO-$, $-CONR_{30}-$; $-NRCONR_{31}-$ or $–NR_{30}COO-$ wherein $R_{30}$ and $R_{31}$ are each H or $C_1 – C_8$ alkyl or cycloalkyl and G is a $C_a(OR_{32})xH_{2a+1-x}$, $C_b(OR32)_yH_{2b-1-y}$, group, $C_cH_{2c+1}$ group, etc. as recited in new claim 16. Clearly, all of these groups when combined with those defined as L will always result in a hydrophilic side chain (L-G)which cannot be construed from or found in the

teachings of Hofmeister et. al. i. e., the claimed compounds due to their chemical nature cannot be regarded as one and the same with those disclosed on the earlier patent and it is therefore respectfully requested that the Examiner's rejection under for double patenting be withdrawn.

Respectfully submitted,

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